Avian Influenza (H5N1)

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It's an average week in your busy practice, when, over the space of a few days, three situations come up:

1. You receive a call from Mrs. Lawrence, one of your regular patients, stating that she plans to visit rural Viet Nam for a month-long trip with her church group. She would like to know what her risks are for contracting avian influenza. "I want to shop in the local markets, Doctor. Is that OK if there are live birds there? Can I eat chicken? What about eggs?"

2. Another patient, Steven Jones, returned from Turkey yesterday and is worried about the recent news of human H5N1 disease reported from that area. He complains of two days of a sore throat, mild cough, and fever with chills. "Do I have bird flu, Doc? Should I come in and see you right away?"

3. When you walk into the exam room, you notice immediately that Lucy Tanghkanaurak appears acutely ill. She has a fever of 102.8 degrees, and she is sneezing and coughing. She complains of severe body aches, non-bloody diarrhea and weakness. You note that her respiratory rate is twenty breaths per minute, and on auscultation of the lungs, you hear rales and rhonchi bilaterally. As you take a history, you discover that she returned five days ago from a trip to Thailand, where she stayed with her relatives and assisted in cooking family-raised poultry. At this point, what do you do?

Physicians in San Diego County can expect to field numerous questions from a concerned public about avian influenza (H5N1) as media coverage of this potential health threat increases. Given the large volume of international traffic to this area, we are also at-risk of seeing imported cases of human H5N1 illness. Part 1 of this article covers key information on recognizing the disease and confirming the diagnosis; Part 2 reviews biologic, epidemiologic, and clinical characteristics.

PART 1: CORE CONCEPTS

Current Case Definition

There are two ways to meet the case definition for suspect avian influenza:

1. Hospitalized patients with:
   - ▶ Radiographically confirmed pneumonia, acute respiratory distress syndrome (ARDS), or other severe respiratory illness for which an alternate diagnosis has not been established
   - ▶ AND travel within 10 days of symptom onset to a country with documented H5N1 avian influenza in birds and/or humans.
   - ▶ Testing for avian influenza A (H5N1) *is indicated* in these patients.

2. Hospitalized or ambulatory patients with:
   - ▶ Documented fever > 100.4° F (38° C)
   - ▶ AND one or more of the following: cough, sore throat, shortness of breath
   - ▶ AND history of contact with poultry (e.g. visited a poultry farm, a house raising poultry, or a bird market) or a known or suspected human case of influenza A (H5N1) in an H5N1-affected country within 10 days of symptom onset.
   - ▶ Testing for avian influenza A (H5N1) should be considered on a case-by-case basis in consultation with local health departments for these patients.

Virologic Diagnostic Techniques

- ▶ A negative rapid antigen test for influenza never rules out avian influenza (H5N1). The average sensitivity of these tests for seasonal influenza is only about 70 percent, and sensitivity may be lower for novel strains of influenza.
- ▶ Collection of specimens for confirmatory testing requires the use of Viral Transport Medium (VTM).
- ▶ One study found a 10-fold higher concentration of the H5N1 virus in the throat than the nasopharynx; therefore, both nasopharyngeal and oropharyngeal specimens should be collected using Dacron or rayon swabs on plastic sticks. Each swab should be placed in a separate vial of VTM and shipped to the laboratory on ice pack.
- ▶ Whenever avian influenza (H5N1) is suspected, the specimen should be sent to the San Diego Public Health Laboratory, not to commercial labs.
- ▶ Because viral culture poses a risk of infection to laboratory workers, it is imperative that the specimen is labeled "SUSPECT AVIAN INFLUENZA." This alerts the lab personnel to perform the diagnostic test of choice for H5N1, which is RT-PCR.
- ▶ The SD PH Lab will process the specimen with the H5 RT-PCR primer once two things have occurred:
  - ▷ The clinician has discussed the case with Community Epidemiology and there is mutual agreement that the patient fits the case definition.
  - ▷ The "Laboratory Specimen Submission Form for Suspect Avian Influenza (H5N1)" has been completed and accompanies the specimen. This form can be downloaded from EMAN (see below); alternatively, Community Epidemiology can fax this form to the clinician's office.

The Role of San Diego Public Health Services, Community Epidemiology Branch

- ▶ Avian influenza (H5N1) is a reportable disease. If you feel you may have a suspect case, call the Community Epidemiology Branch immediately, 24 hours a day, 7 days a week:
  - ▷ M– F, 8AM–5PM: (619) 515-6620
  - ▷ After business hours and on weekends: Station M (858) 565-5255
- ▶ Subscribing to the online San Diego Emergency Medical Alert Network (EMAN) will help you stay abreast of the local infectious disease developments, including avian influenza. The case screening, case report and specimen submission forms can be downloaded from the EMAN site.
- ▶ To subscribe to EMAN, go to: www.emansandiego.com.

Case Scenarios Revisited

1. Mrs. Lawrence should be told that as of February 27, 2006, there are no travel restrictions to countries with human H5N1 disease (updated information for travelers may be found at www.cdc.gov/travel/other/avian_influenza_se_asia_2005.htm). During her stay in Viet Nam, care should be taken to avoid contact with live, well-appearing, sick, or dead poultry and with any surfaces that may have been contaminated by poultry or their feces or secretions. Live bird markets should be avoided. Prohibited activities include food preparation that involves raw poultry. Influenza viruses are readily killed at cooking temperatures. While eating thoroughly cooked poultry products has not been associated with disease, she should avoid eating undercooked, bloody-appearing poultry or eggs with runny yolks.

2. The correct advice for Steven Jones depends on whether he was exposed during the right time frame (within ten days of symptom onset) and whether he engaged in any high-risk behavior as listed in the second part of the case definition. Community Epidemiology will review the case specifics with you and make recommendations. If it is decided that this individual is at risk for avian influenza, he should receive further evaluation in a hospital emergency department setting, and the department should be notified ahead of time to expect him. Ideally, he should not sit in a common waiting room but should be given a surgical mask on entry and taken immediately to a private examination area.

   Had Mr. Jones already been in your office when you obtained his history, then again, a call

and Your Practice

to Community Epidemiology will help you determine whether he meets part two of the case definition. If so, then a rapid antigen test and, more importantly, nasopharyngeal and oropharyngeal specimens should be taken, with the latter sent in viral transport medium (VTM) on ice pack to the Public Health lab. Clinic staff should use personal protective equipment (PPE) when caring for Mr. Jones.

3. Ms. Tanghkanaurak is likely to fit part one of the case definition for avian influenza (H5N1): her pneumonia has not been radiographically confirmed but you have a strong suspicion clinically. Clinic staff should use PPE, and a surgical mask should be placed on the patient if she can tolerate it. Family members and/or paramedics who will transport her to a hospital emergency department should also wear PPE, and the hospital should be advised ahead of time that a patient with suspected H5N1 disease is on the way. Community Epidemiology should be notified immediately.

Contact with the Community Epidemiology Branch of San Diego County Public Health Services should be the clinician's first step when avian influenza (H5N1) is suspected.

PART 2: REVIEW OF THE DISEASE

Infectious Agent

- An orthomyxovirus that contains a single-stranded segmented RNA genome prone to replication errors leading to a high rate of mutation.
- Subgroup identification is based on the properties of surface glycoproteins: hemagglutinin (H) and neuraminidase (N).
- H1 and H3 are the current circulating seasonal (human) influenza subtypes. Since 1997, highly pathogenic avian influenza (H5N1) has caused sporadic illness in man with high mortality rates.

Reservoir

- Migratory aquatic waterfowl are generally asymptomatic carriers of various avian influenza strains, but recently there have been a number of large wild bird die offs due to H5N1, an unusual phenomenon.
- Domestic poultry may become infected after co-mingling with wild birds or swimming in the same bodies of water; H5N1 may be highly pathogenic to these birds, causing rapid mortality.

The distribution of the disease in birds and humans is rapidly evolving. The following sections are based on information available as of February 2006.

Geographic Distribution

- No human or avian cases of H5N1 are currently known to exist in North America.
- Since 2004, gradual east-to-west spread of the virus from its origins in Southeast Asia has followed the migration paths of wild birds. Countries in the Middle East, the Indian subcontinent, Europe, and Africa have reported infected bird populations.
- As of February 27, 2006, the World Health Organization reported 171 laboratory-confirmed cases of human H5N1 disease and 93 deaths worldwide. The countries involved are Cambodia, China, Indonesia, Iraq, Thailand, Turkey, and Viet Nam. Viet Nam has been the hardest hit, with 93 human cases and 42 deaths.
- The Asian migratory bird flyway overlaps with the North American flyway in Alaska, creating the possibility that North American migratory birds will eventually become infected.

Modes of Transmission and Infection Control

- High-risk activities include butchering, defeathering, and otherwise handling diseased birds, suggesting that close contact is required. Unusual practices, such as using the mouth to suck bloody secretions out of a fighting cock's beak have also been reported to induce illness.
- Children playing in areas contaminated by infected poultry waste have become ill, and the virus may remain viable in feces for up to 30 days in low temperature conditions, suggesting that infection may be transmitted by fomites and hand to mucous membrane contact.
- There is an anecdotal report of two cases that may have resulted from drinking raw duck's blood. All influenza viruses are killed at normal cooking temperatures; there have been no epidemiologic links between the disease and consumption of well-cooked poultry products.
- At this time, human-to-human transmission appears to be an exceedingly rare event: Almost all cases have had contact with diseased birds. In one exceptional case in Thailand, a mother provided physical care to her ill child for several days then became sick without other risk factors for infection.
- In the event of the development of human-to-human transmission, it is likely that droplet transmission would predominate as it does for seasonal influenza. Close contact within three feet of the patient or the transfer of virus with the hands to mucous membranes poses a risk.
- Because there is sparse evidence for airborne transmission of seasonal influenza within crowded populations in enclosed spaces such as airplanes, the possibility of this route of transmission for avian influenza (H5N1) cannot be excluded at this time.
- At minimum, droplet precautions should be enforced when caring for a patient with suspect or confirmed H5N1 disease. This includes the use of a surgical mask when in the room with the patient, eye protection when there is risk of splatter of secretions on to mucous membranes, and gown and gloves for any physical contact.
- An N95 mask has been recommended for aerosolizing procedures, such as intubation, nebulizer treatments, bronchoscopy, and suctioning. More conservative recommendations would be to use an N95 mask for the routine care of a suspect or confirmed case of H5N1 disease.
- Viable H5N1 virus has been recovered from the blood and stools of humans with the disease; therefore, bloodborne and enteric precautions should also be in effect.

Incubation Period

- Between 48 hours to a week. Preliminary data suggest that the incubation period for H5N1 may be longer than the typical two days of seasonal influenza, but estimation is uncertain because in most cases exposure to poultry was ongoing.

Period of Communicability

- Because human-to-human transmission of avian influenza (H5N1) has not yet begun, this is unknown.
- If H5N1 disease follows the pattern of seasonal influenza, adult patients may be contagious a day or two before symptom onset; peak viral shedding occurs within two to three days of symptom onset and parallels the fever curve. In adults, viral shedding ends three to five days from clinical onset.
- Children may shed seasonal influenza virus up to five days prior to symptom onset, have higher viral titers and shed virus longer than adults: in one study, 5 percent of children continued to shed virus two weeks after the onset of their illness.
- Immunocompromised persons also shed virus for a prolonged period.

Patterns of Susceptibility

- Because influenza pandemics are caused by novel influenza strains, to which all humans are immunologically naïve, attack rates are generally 25 percent or more in all age groups.

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- In contrast to seasonal influenza, where the highest morbidity and mortality occur in the very young and the very old, pandemic influenza causes increased deaths in young adults. This was especially pronounced in the 1918 pandemic, where nearly one half of influenza-related deaths occurred in persons 20 to 40 years old.
- Deaths from H5N1 disease have likewise occurred principally in children and young adults; whether this indicates an innate enhanced susceptibility amongst these age groups or reflects age-related increased risk behaviors (or both) is yet to be determined.
- Temporal distribution differs between pandemic and seasonal influenza. Whereas seasonal influenza occurs mainly during winter in temperate zones, pandemic influenza may occur at any time of year.
- Often, pandemic influenza strikes as a series of successive outbreaks, each lasting for a couple of months, then subsiding only to recur several months later. The 1918 pandemic had three waves within approximately one year; the second wave was by far the most severe in terms of morbidity and mortality.

Clinical Spectrum

- Initially, H5N1 disease closely resembles seasonal influenza, with sudden onset of high fever, headache, myalgias, and cough. Possible early distinguishing features include the following (but the absence of these should not discourage you from considering the diagnosis):
  - Fewer upper respiratory symptoms
  - A greater incidence of watery diarrhea in children and adults
- The clinical course involves rapid progression to lower respiratory tract disease, with most patients reporting shortness of breath in the first week of illness. Tachypnea, respiratory distress, and inspiratory crackles are common, with variable production of sputum that may be bloody.
- Radiographic abnormalities usually also develop in the first week, with the most common finding being multifocal or patchy infiltrates, sometimes with an interstitial component.
- When respiratory failure develops the typical ground glass pattern of ARDS on chest X-ray is frequently seen.
- Respiratory failure may be followed by multiorgan failure, especially targeting the heart and kidneys.
- Although a single case report of diarrhea without respiratory symptoms and two case reports of encephalitis without respiratory symptoms have been published, the presentation has been primarily a respiratory illness.
- The case fatality rate is approximately 50 percent; however, this is calculated solely from patients who had sufficiently severe symptoms to seek medical attention; there is some evidence that mild and asymptomatic infection occur. Population-based seroprevalence studies in areas with human disease are urgently needed to determine the true case fatality rate.
- In contrast to prior pandemics, most deaths from H5N1 disease have resulted from primary viral pneumonia, not from superinfection with a bacterial pathogen.
- Death often occurs within two weeks of the onset of illness.

Non-specific Laboratory Findings

- Common abnormalities include:
  - Leukopenia, especially lymphopenia
  - Mild to moderate thrombocytopenia
  - Mild to moderate elevation of aminotransferases
- Less frequently, a picture compatible with disseminated intravascular coagulation results.
- Severe lymphopenia and thrombocytopenia have been indicative of a worse prognosis.

Treatment

- The neuraminidase inhibitors, oseltamivir and zanamivir, may be effective in ameliorating the disease if instituted within 48 hours of onset of the illness; however, higher doses and longer treatment courses may be required than for seasonal influenza. Oseltamivir has not been particularly impressive so far in human H5N1 disease, but it has often been instituted fairly late in the clinical course.
- In one fatal H5N1 case in Viet Nam in which oseltamivir was used, the virus mutated from drug-susceptible to drug-resistant within a period of days. Thirteen other drug-resistant cases in Viet Nam have been reported.
- It is estimated that once the pandemic strain is known, it will take about six months to develop the pandemic vaccine. Other measures, such as traditional epidemiologic disease management techniques and the use of antiviral drugs, can be looked at as a way of "buying time" until the pandemic vaccine is widely available.
- Given universal immunologic naivete to the H5N1 strain, induction of immunity will probably require two shots given one month apart.

Pandemic Potential

- Three conditions must be present to initiate an influenza pandemic:
  1. The virus must be a novel one, to which there is a uniform lack of protecting antibodies in humans worldwide
  2. The virus must be highly pathogenic to man
  3. The virus must transmit in a sustained fashion between humans
- The H5N1 virus has achieved the first two of these properties, and its predilection for high mutation rates creates concern that it will achieve the third characteristic soon. Mammal-to-mammal transmission has recently been observed in tigers, ferrets, and household cats.
- The development of efficient human-to-human transmission could occur via one of two mechanisms:
  1. A series of adaptive mutations. A pandemic induced by this mechanism would likely begin with small clusters of human-to-human transmission that are controllable with traditional epidemiologic surveillance, case management, and contact tracing. Quarantine and isolation would be important means of limiting spread of the disease.
  2. Genetic reassortment, the exchange of genetic material between avian and human strains, could lead to sudden shifts in transmissibility and virulence, creating an explosive pandemic and giving us less opportunity to limit spread. Reassortment could occur in "mixing vessel" hosts, such as pigs or man, if an individual acquired simultaneous infections with both viruses.

Additional Measures for Pandemic Preparation

- Educational reinforcement about hand-washing and using tissues to cover the nose and mouth when coughing or sneezing is as important for avian influenza as it is for seasonal flu.
- Even though the seasonal flu vaccine will not protect against the pandemic strain, it is a valuable adjunct to protect the population against pandemic influenza for the following reasons:
  - A low prevalence of seasonal influenza in the community would reduce the likelihood of co-infection with seasonal and pandemic flu strains, which could lead to dangerous reassortment events.
  - A low prevalence of seasonal influenza in the community would reduce confusion in the epidemiologic investigation of pandemic influenza.
  - Seasonal influenza causes over 100,000 hospitalizations in the U.S. every year. A low prevalence of seasonal influenza would reduce stress on a healthcare system already overburdened by the pandemic. The vaccination of healthcare workers, historically a group with low vaccine coverage, has been demonstrated to reduce morbidity and mortality from seasonal influenza in high-risk patients.
- In prior pandemics, death from secondary bacterial pneumonia was a common complication, so the promotion of pneumococcal vaccine in susceptible persons is recommended.